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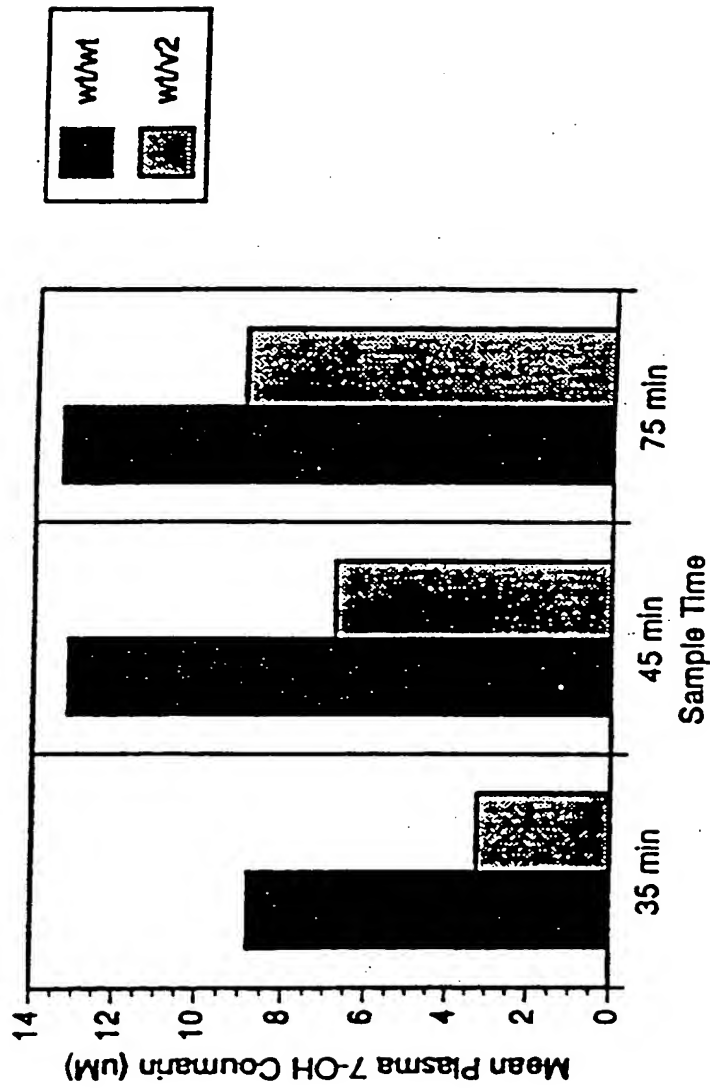
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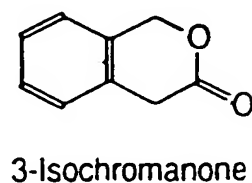
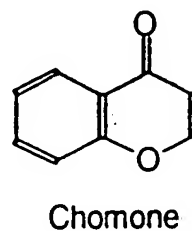
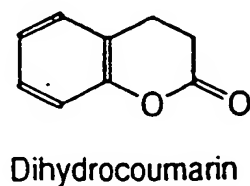
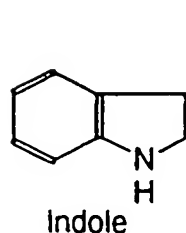
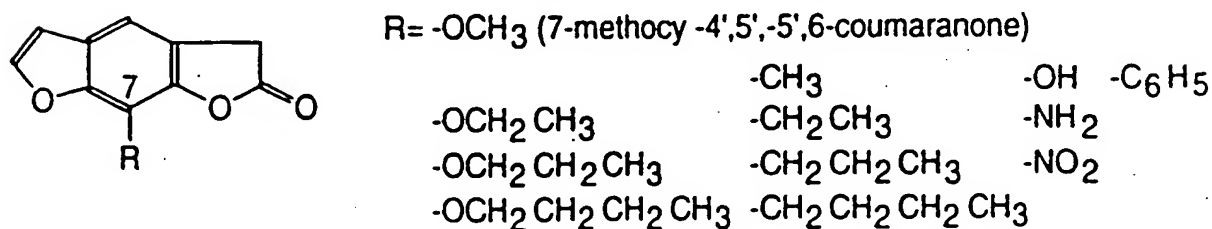
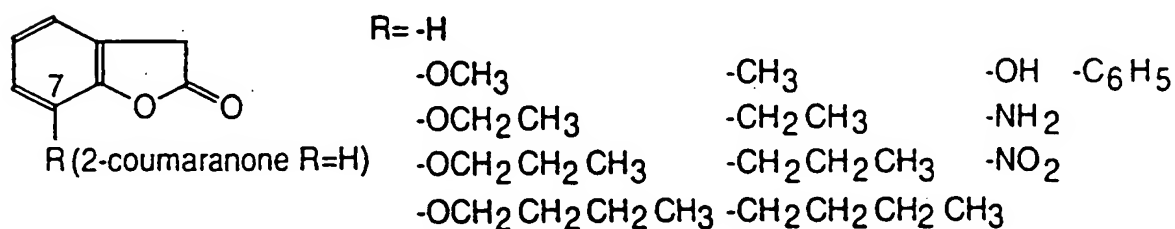
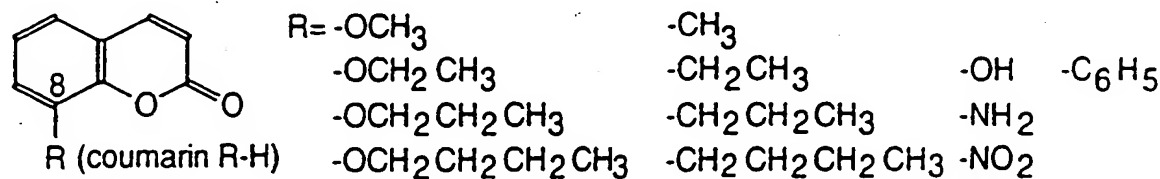
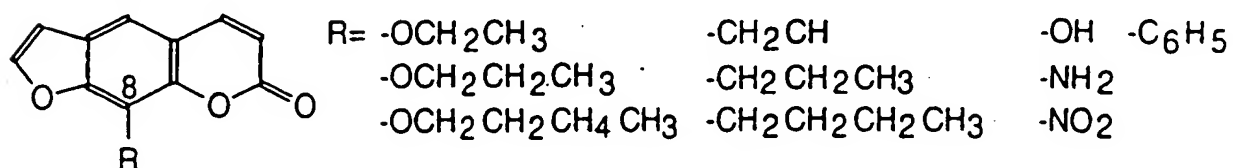
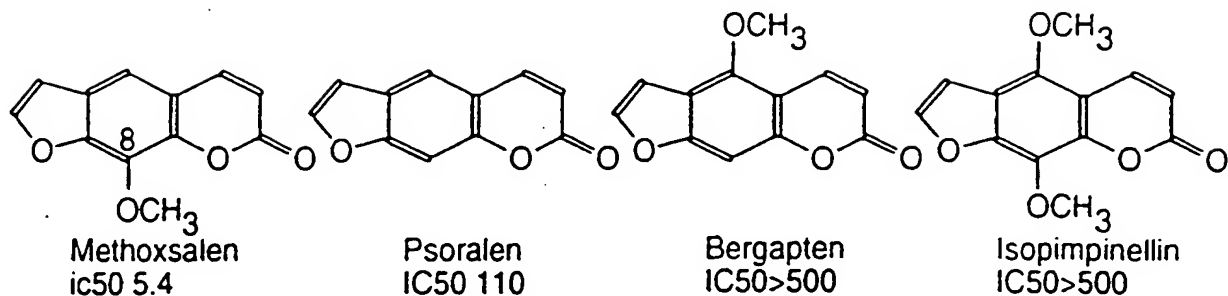
FIGURE 1

Heterozygous CYP2A6 individuals have lower CYP2A6 activity than wild type/wild type (wt) individuals

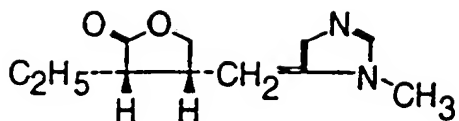


Application of a method to characterize CYP2A6 activity in human subjects by taking plasma samples at times as early as 35 minutes after administration of an oral dose of coumarin (100 mg in this example). Lower doses of coumarin may also be used and the data can also be expressed as a ratio of coumarin/7-OH coumarin. The test can also be performed using oral nicotine or another CYP2A6 substrate.

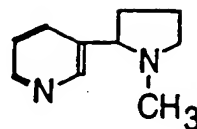
2/23  
FIGURE 2A



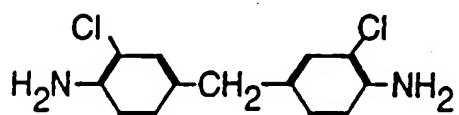
3/23  
**FIGURE 2B**



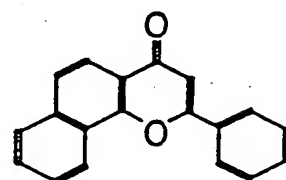
Pilocarpine



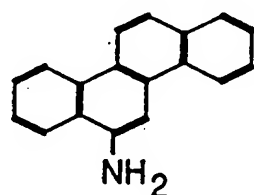
Nicotine



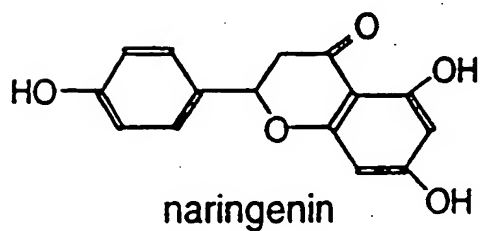
4,4'-Methylene bis[2-chloroaniline]



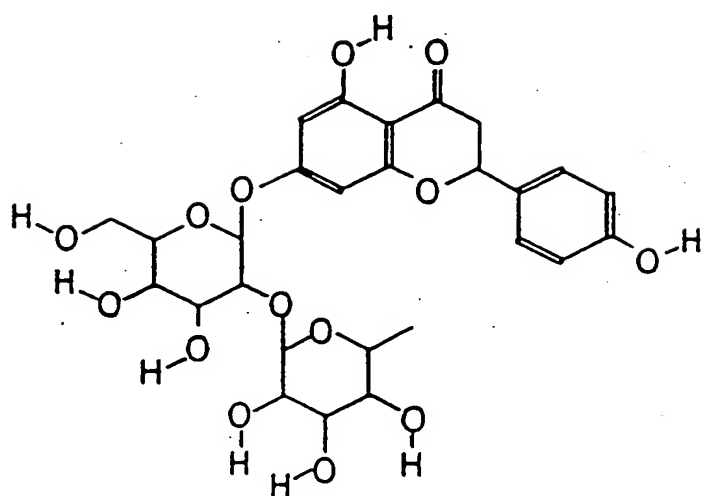
6-Aminochrysene



α-Naphthoflavone

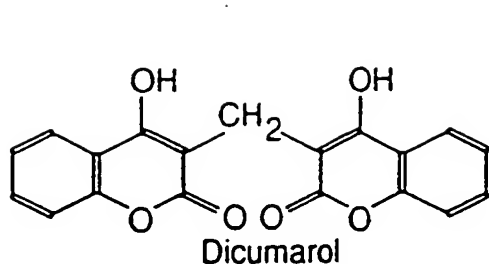


naringenin

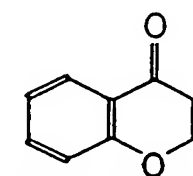


naringin

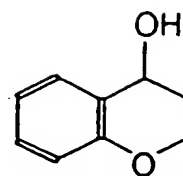
4/23  
FIGURE 2C



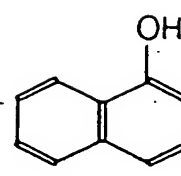
About 80% activity left at 0.05 mM concentration



4-Chromanone

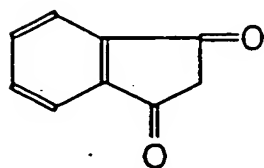


4-Chromanol

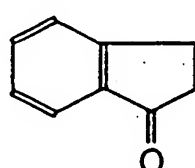


1-Naphthol

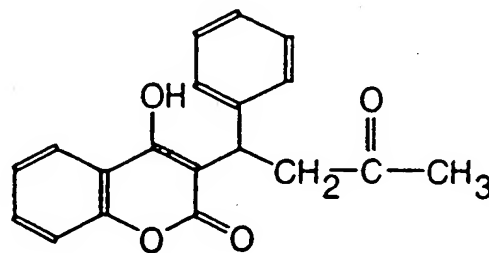
70% inhibition at  
 0.5 mM concentration



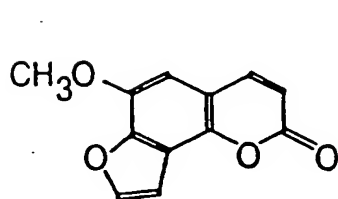
1,3-Indandione



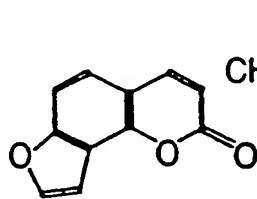
1-Indanone



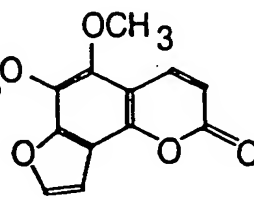
Warfarin



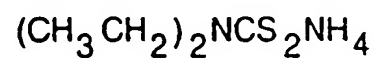
Sphondin  
 IC50 90



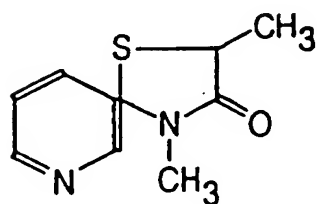
Amgelicin  
 IC 50 160



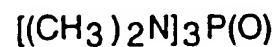
Pimpinlin  
 IC50>500



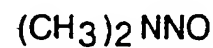
Diethyldithiocarbamic acid  
 ammonium salt



SM-12502



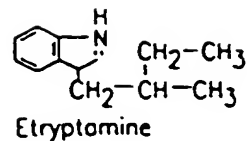
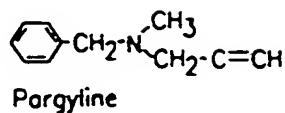
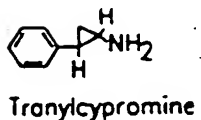
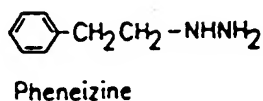
Hexamethylphosphoramide



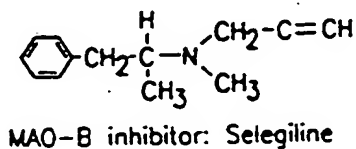
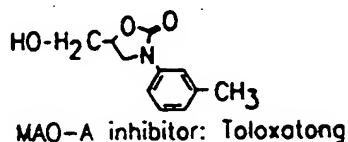
N-Nitrosodimethylamine

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**FIGURE 2D**

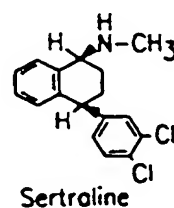
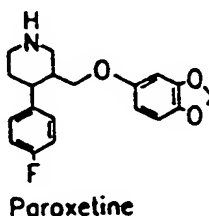
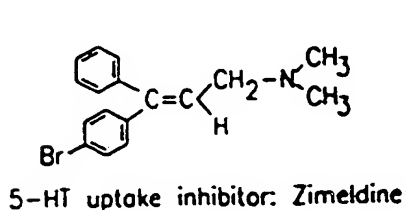
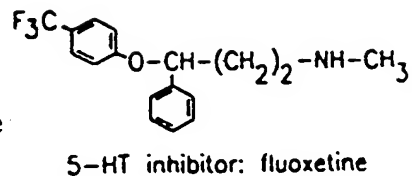
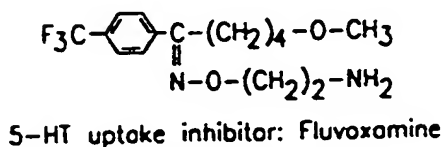
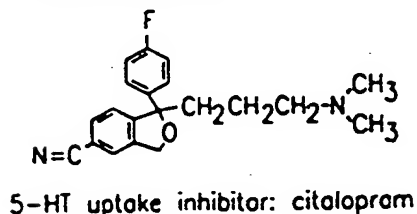
Non-selective MAO inhibitors



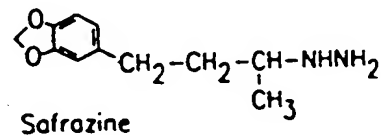
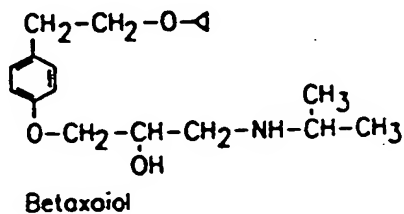
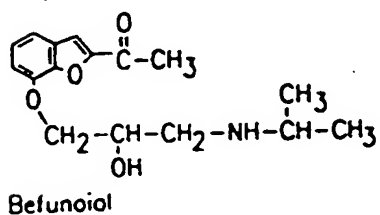
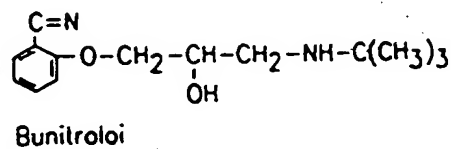
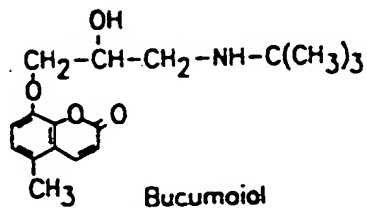
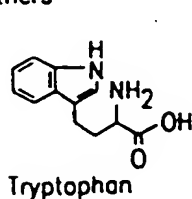
Selective MAO Inhibitors



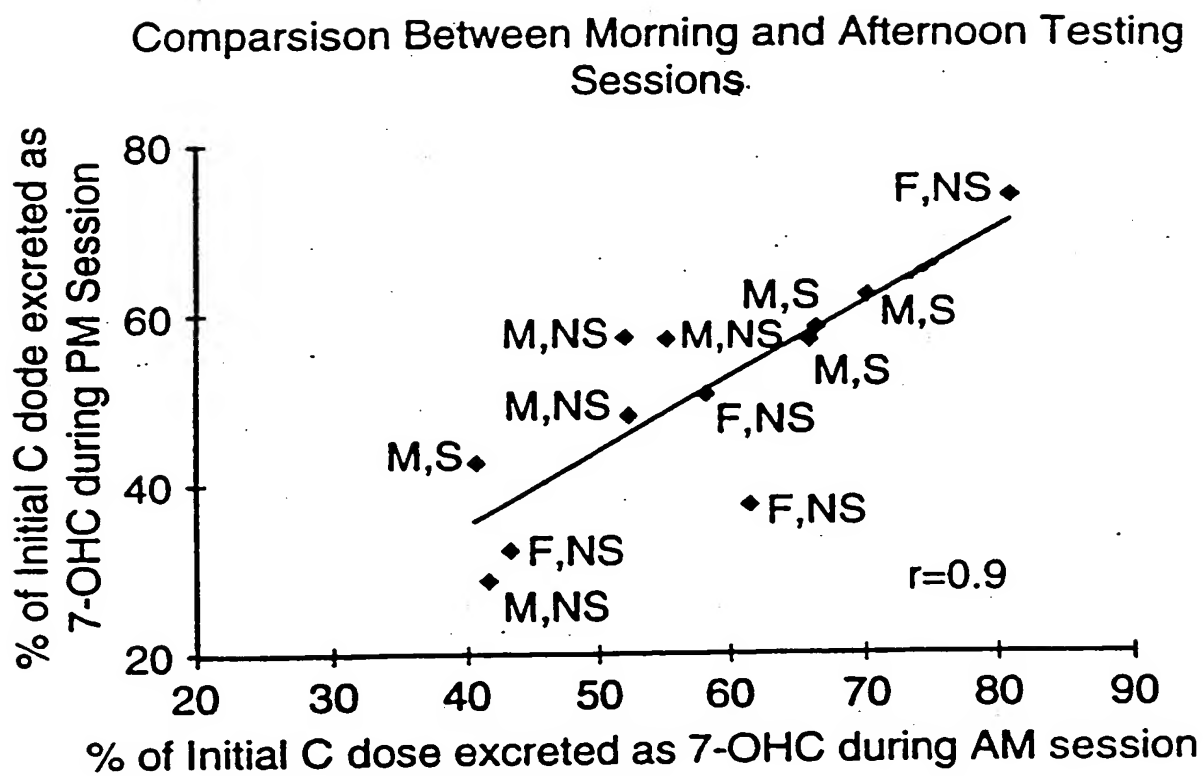
Antidepressants



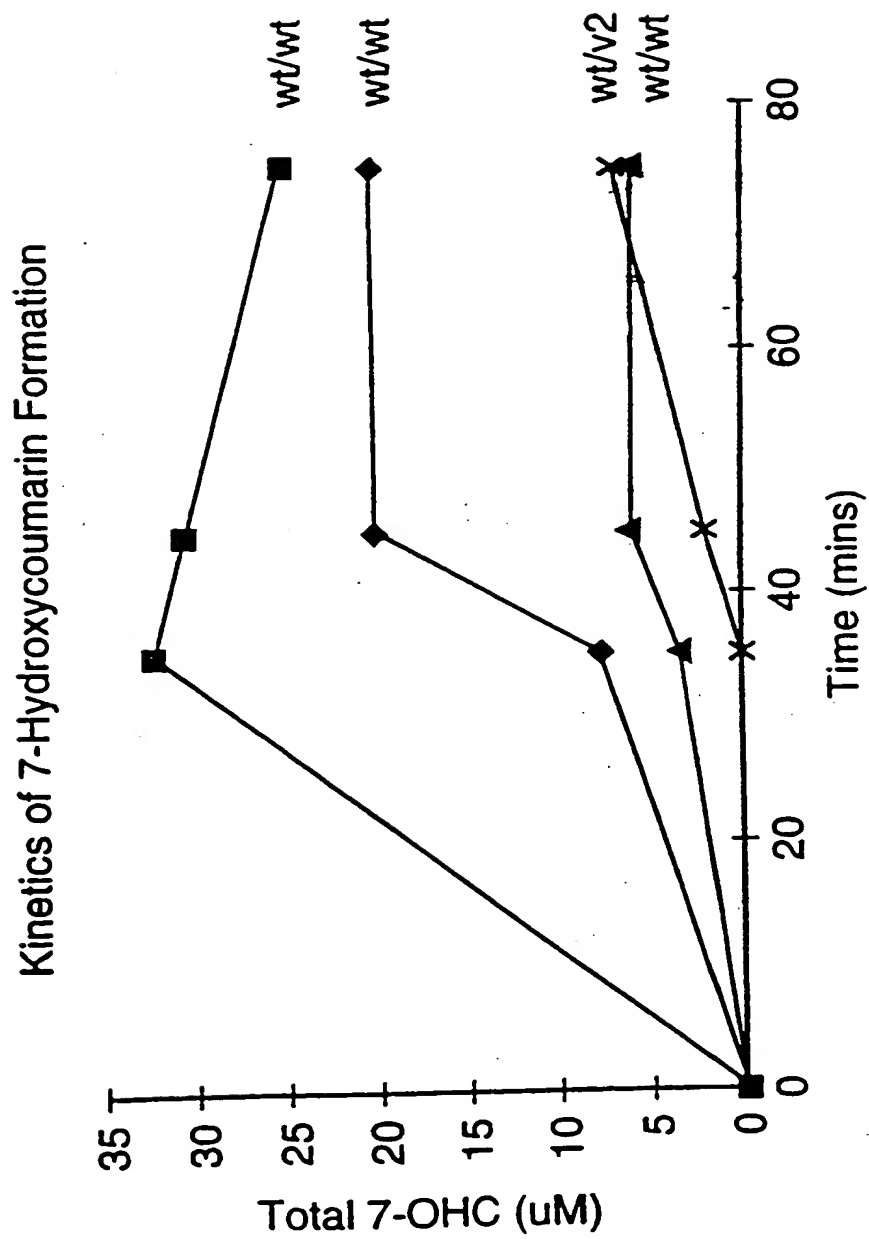
Others



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FIGURE 3

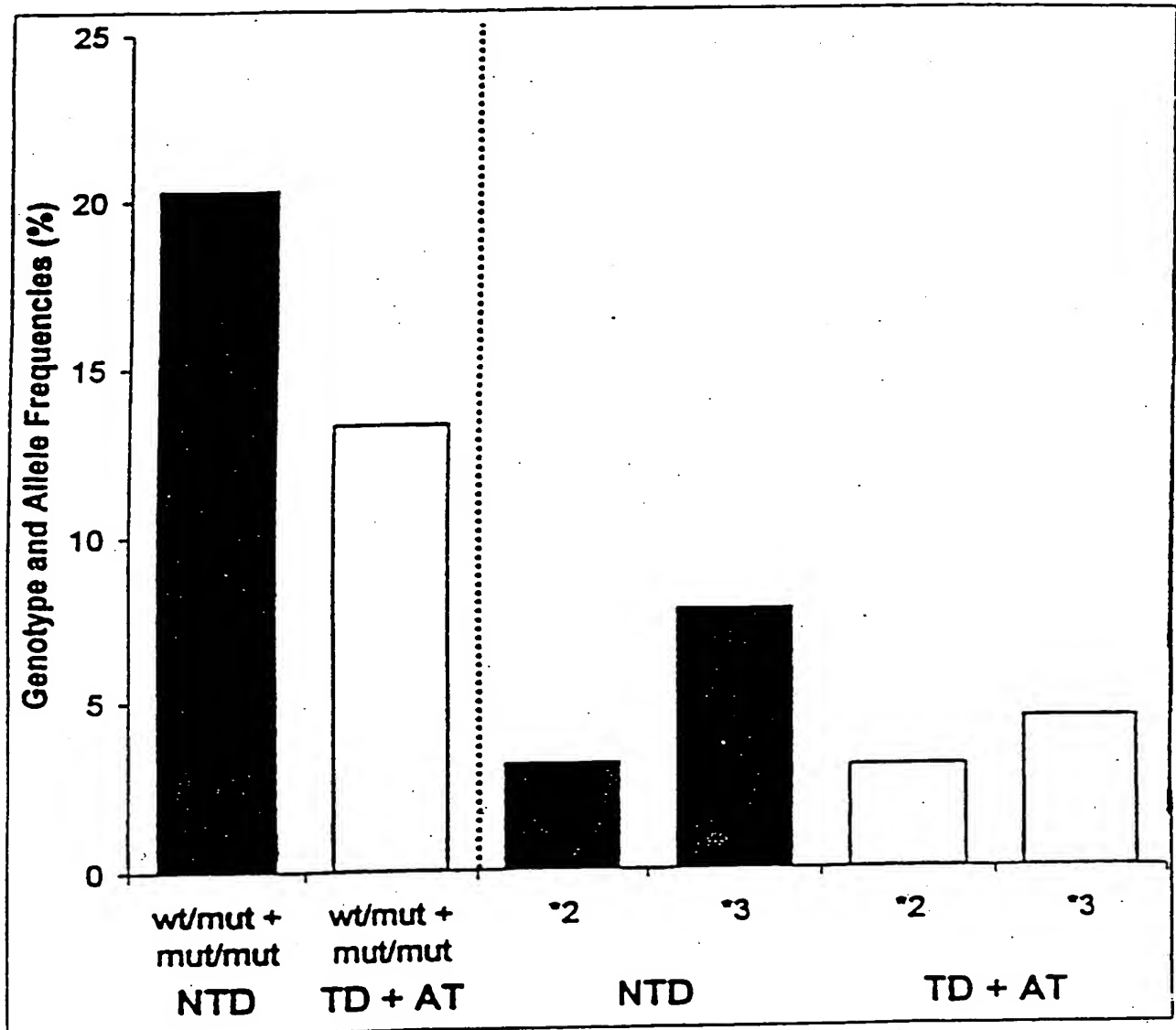


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FIGURE 4



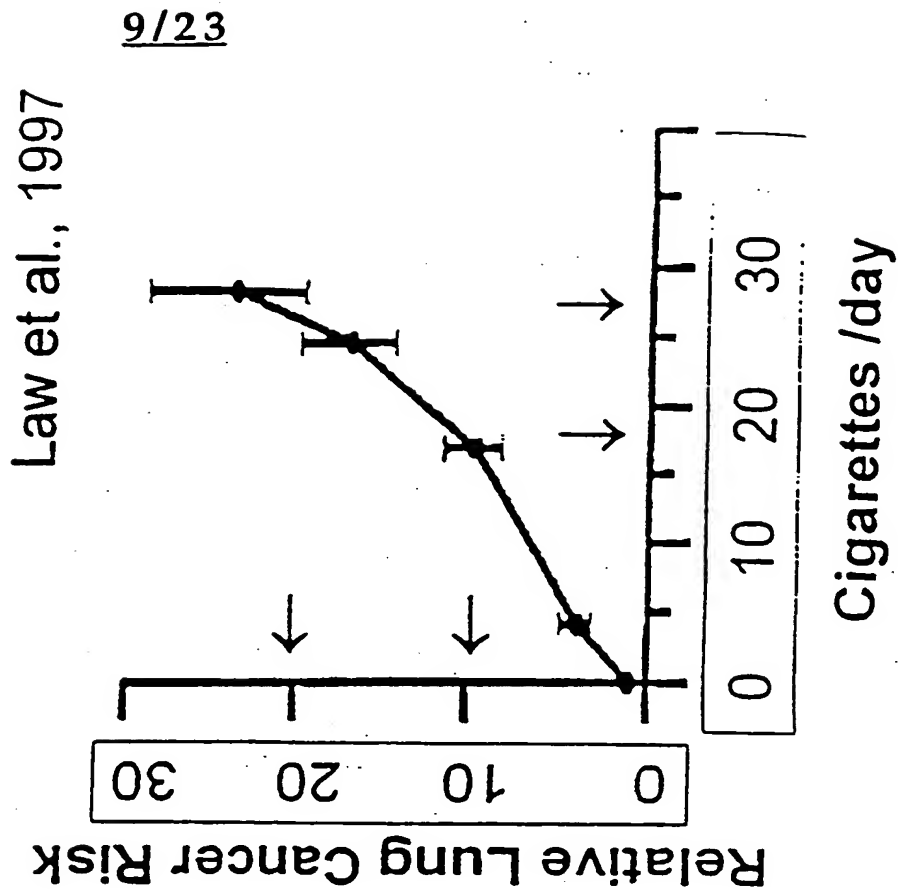
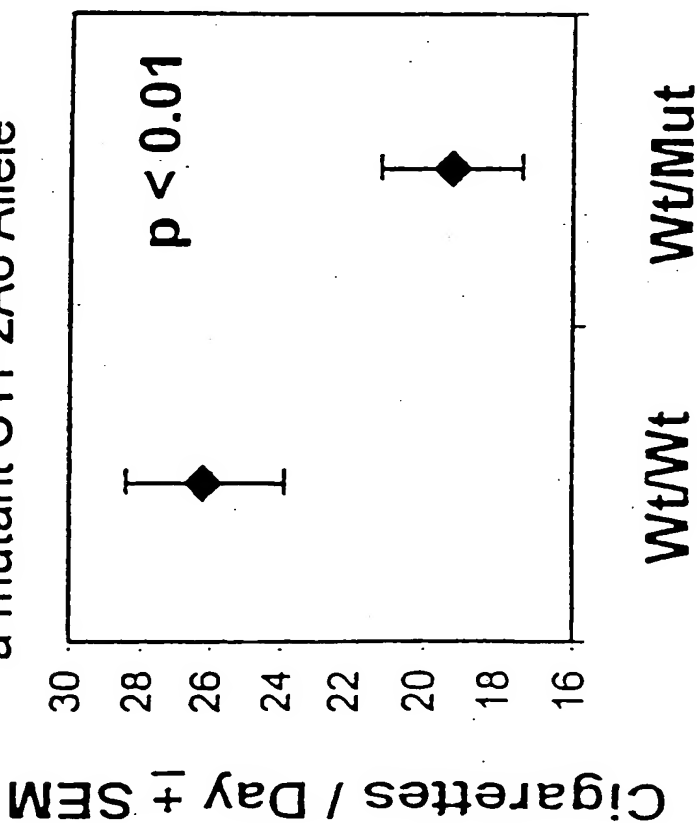


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FIGURE 5



**FIGURE 6**

Tobacco Used by Smokers  
without (wt/wt) or with (wt/mut)  
a mutant CYP2A6 Allele



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FIGURE 7

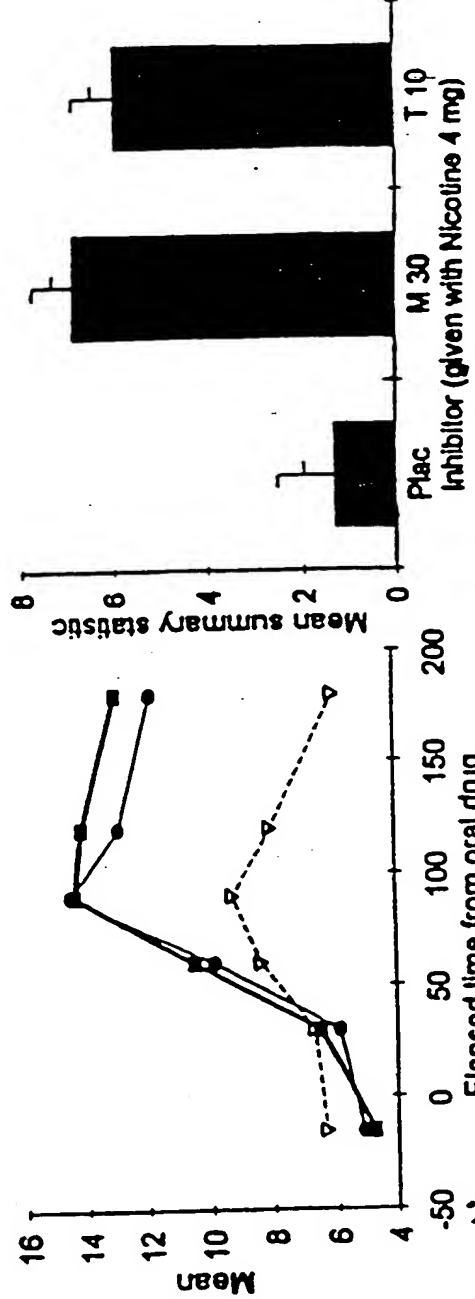
Plasma nicotine, ng/ml

Comparison	F	p	Significant drug-vs-drug differences
Main effect of drug	21.830	0.000	M 30
Main effect of sex	1.480	0.252	Plac
Drug*sex interaction	1.250	0.309	M 30
			T 10

0.0001

0.0001

Post-drug mean minus baseline



Placebo  
Methoxsalen 30 mg  
Tranylcypromine 10 mg

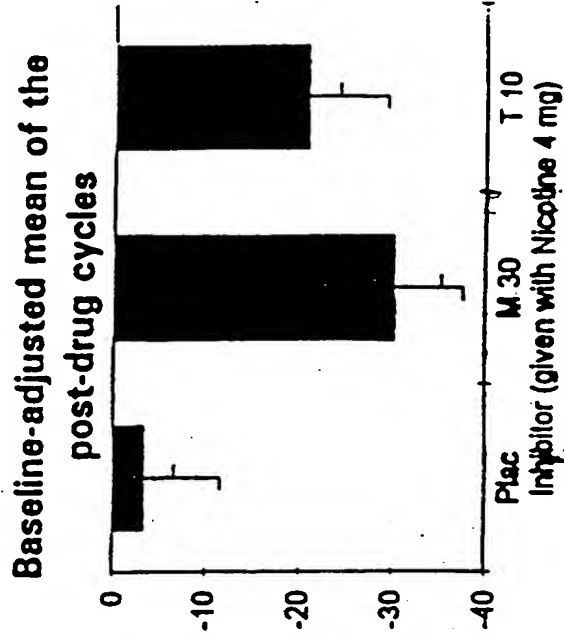
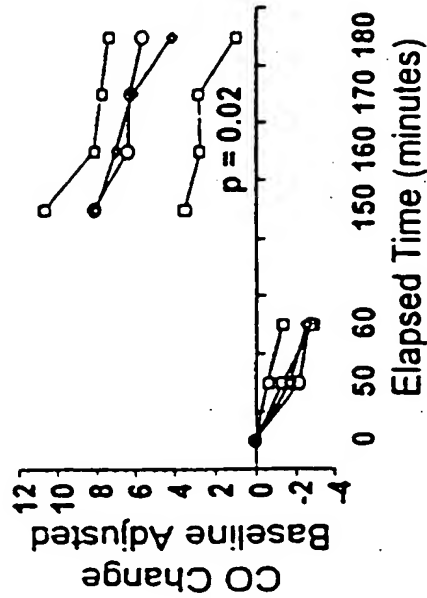
Means are shown with standard errors

FIGURE 8

## Current desire to smoke

Comparison	F	P	Significant drug-vs-drug differences	
Main effect of drug	8.220	0.003 **	M 30	T 10
Main effect of sex	2.190	0.170	Plac	
Drug*sex interaction	3.390	0.054	M 30	0.0171
			T 10	

## Baseline-adjusted mean of the post-drug cycles



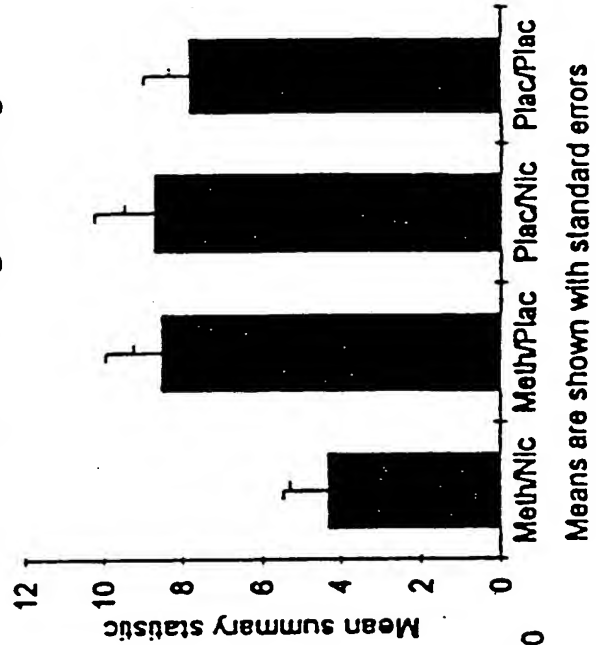
Means are shown with standard errors

FIGURE 9

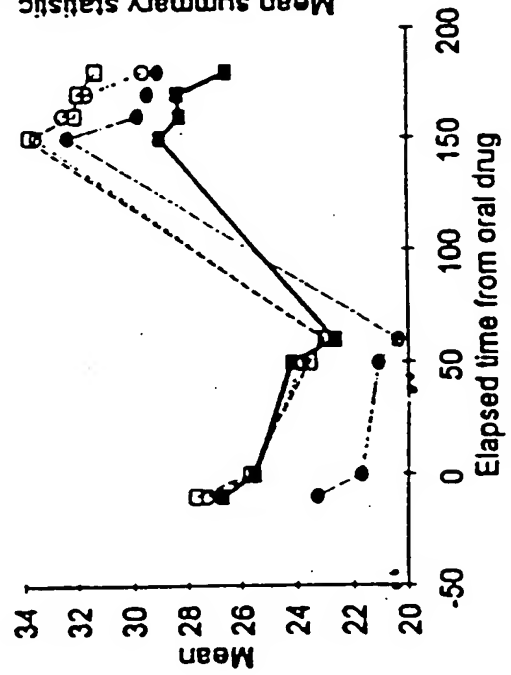
Carbon monoxide, parts/million

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.880	0.022 *				
Main effect of sex	0.380	0.554				
Drug*sex interaction	1.370	0.277				
Meth/Nic vs others	11.380	0.003 **	Meth/Nic	0.0078	Plac/Nic	0.0204
			Meth/Plac	0.0082	Plac/Plac	
Among others	0.100	0.904				

Increase during smoking



Means are shown with standard errors

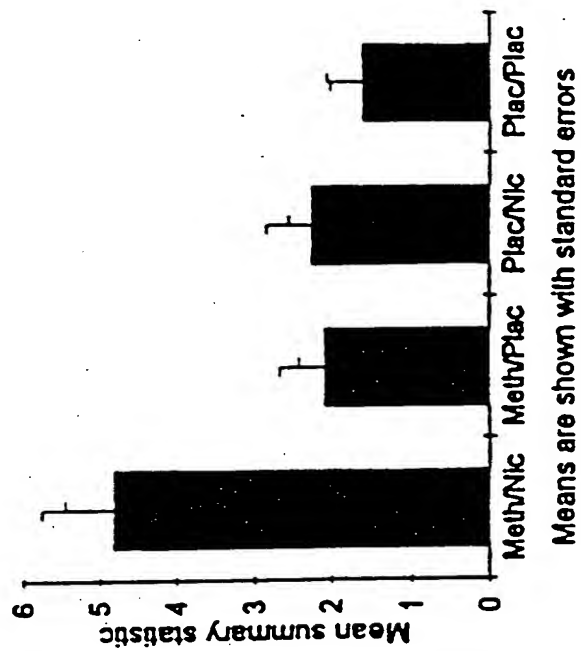


Legend: Meth/Nic (solid line, filled circles), Meth/Plac (dashed line, open squares), Plac/Nic (dotted line, filled circles), Plac/Plac (dash-dot line, open circles)

**FIGURE 10**

**Ratio of plasma nicotine increase to CO increase during smoking**

Comparison	F	p	Significant drug-vs-drug differences		
Main effect of drug	5.810	0.004 **	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	1.620	0.235	Meth/Nic	0.0039	0.0061 0.0008
Drug*sex interaction	0.800	0.506	Meth/Plac		
			Plac/Nic		
Meth/Nic vs others	16.720	0.000 **			
Among others	0.380	0.689			



**FIGURE 11**

**Number of cigarettes smoked**

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.670	0.026 *	Meth/Nic	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	0.470	0.509				
Drug*sex interaction	1.490	0.243				
Meth/Nic vs others	7.510	0.011 *				
Among others	1.860	0.177				

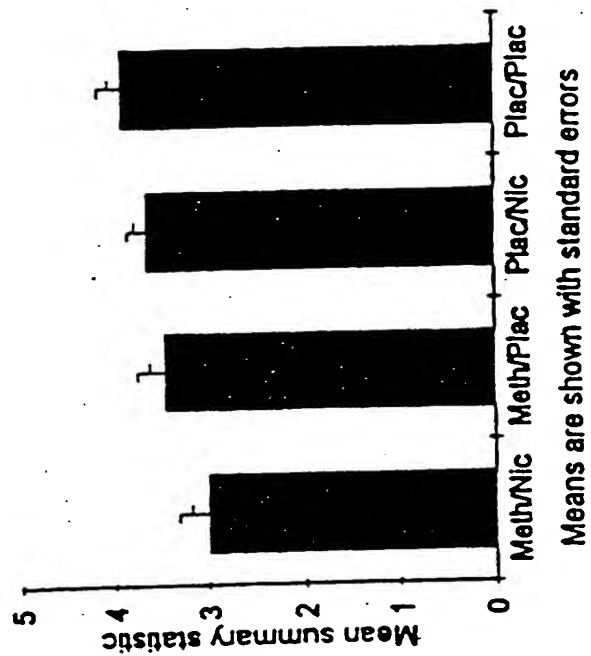
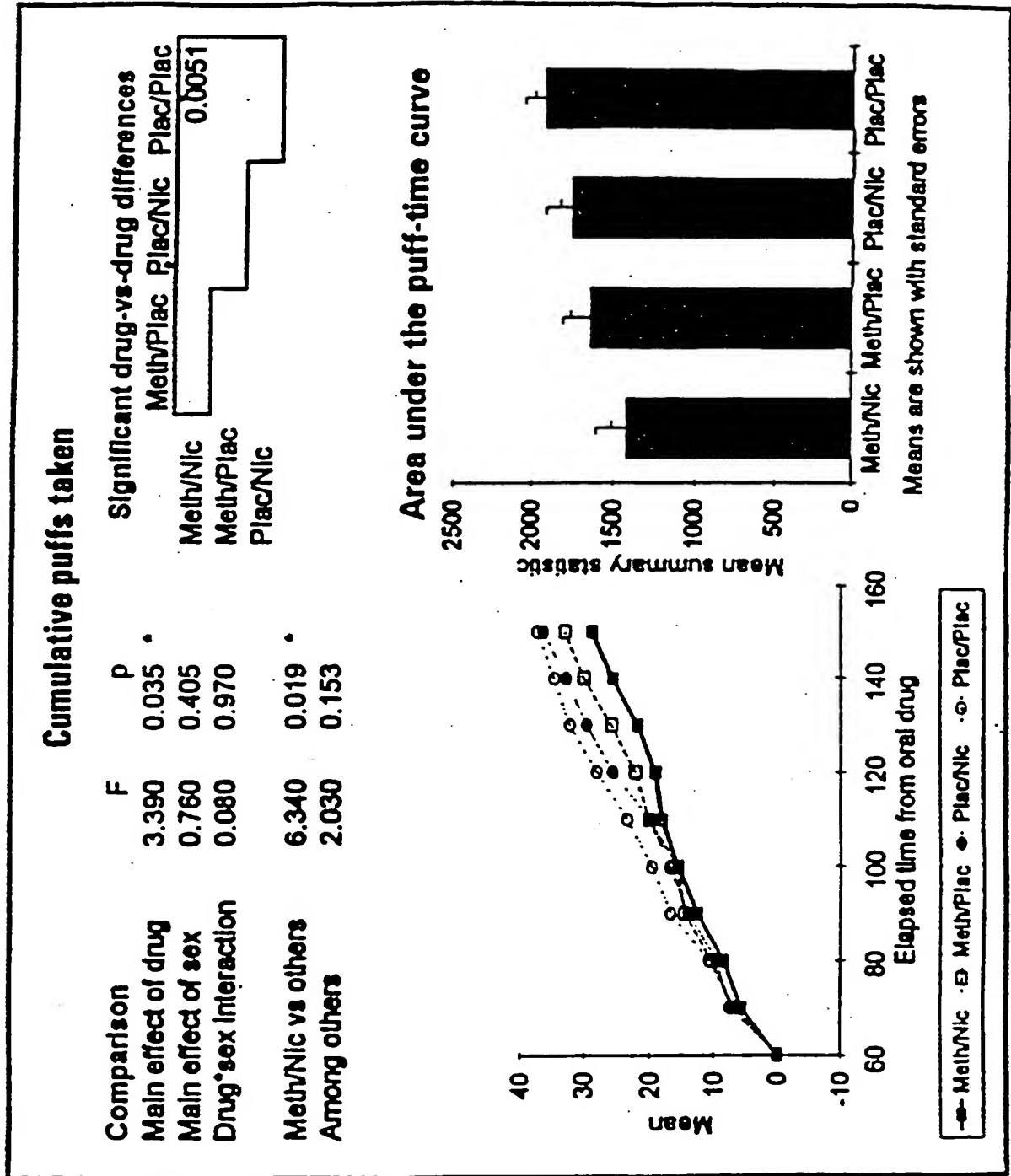


FIGURE 12





**FIGURE 13**

**Number of grams of tobacco burned**

Comparison	F	p	Significant drug-vs-drug differences
Main effect of drug	3.230	0.040 *	Meth/Plac Plac/Nic Plac/Plac
Main effect of sex	3.290	0.103	Meth/Nic 0.0282
Drug*sex interaction	1.140	0.355	Meth/Plac 0.0079
			Plac/Nic
Meth/Nic vs others	8.930	0.006 **	
Among others	0.380	0.687	

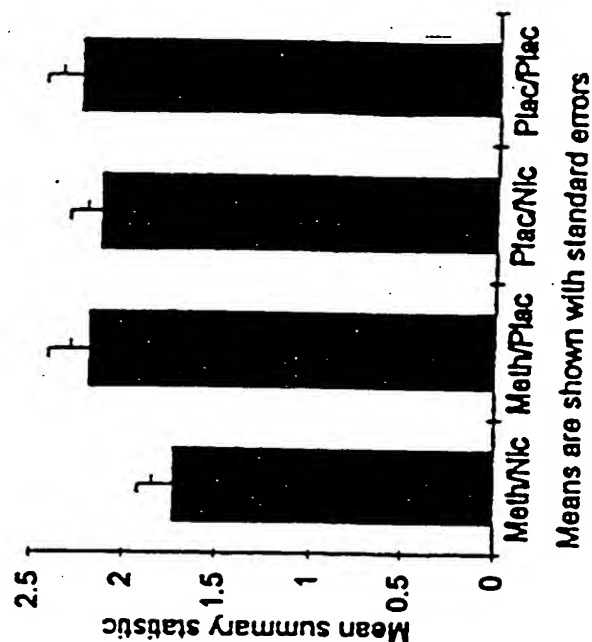
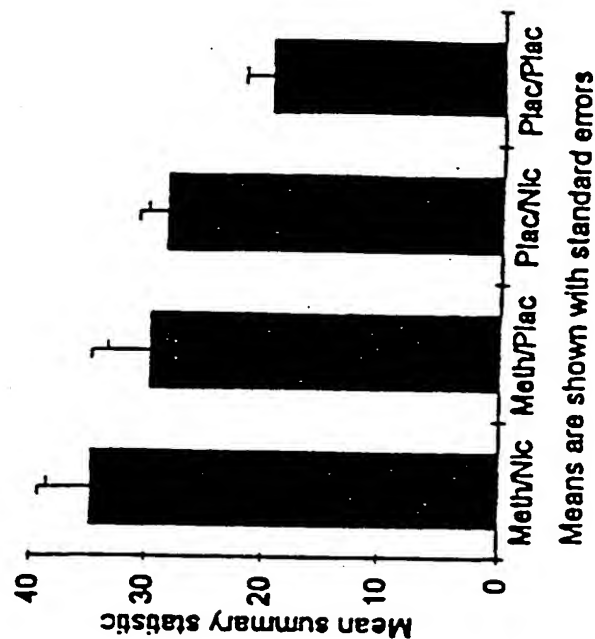


FIGURE 14

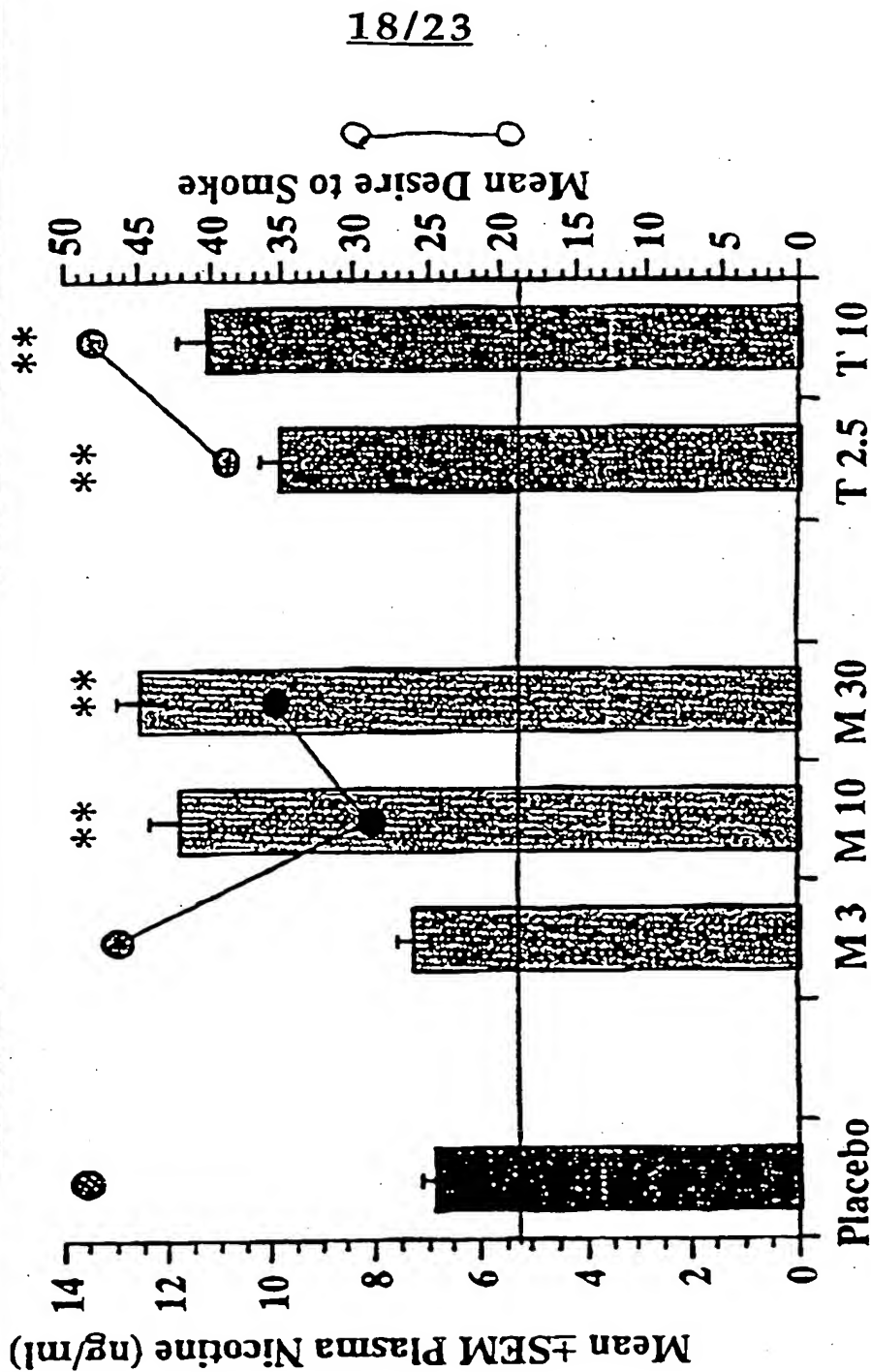
### Latency between first two cigarettes, minutes

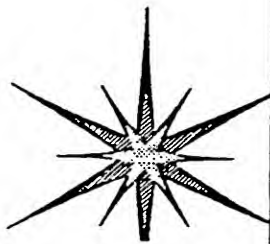
Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	2.820	0.060	Meth/Nic	Plac/Nic	Plac/Plac	Plac/Plac
Main effect of sex	0.810	0.392				
Drug*sex interaction	0.170	0.914				
Meth/Nic vs others	3.950	0.059				
Among others	2.350	0.117				



**FIGURE 15**

# **Methoxsalen and Tranlycypromine Increase Oral Nicotine Bioavailability and Decrease Desire to Smoke**





**FIGURE 16**

# Extracts of St. John's Wort Inhibit Nicotine Metabolism in vitro

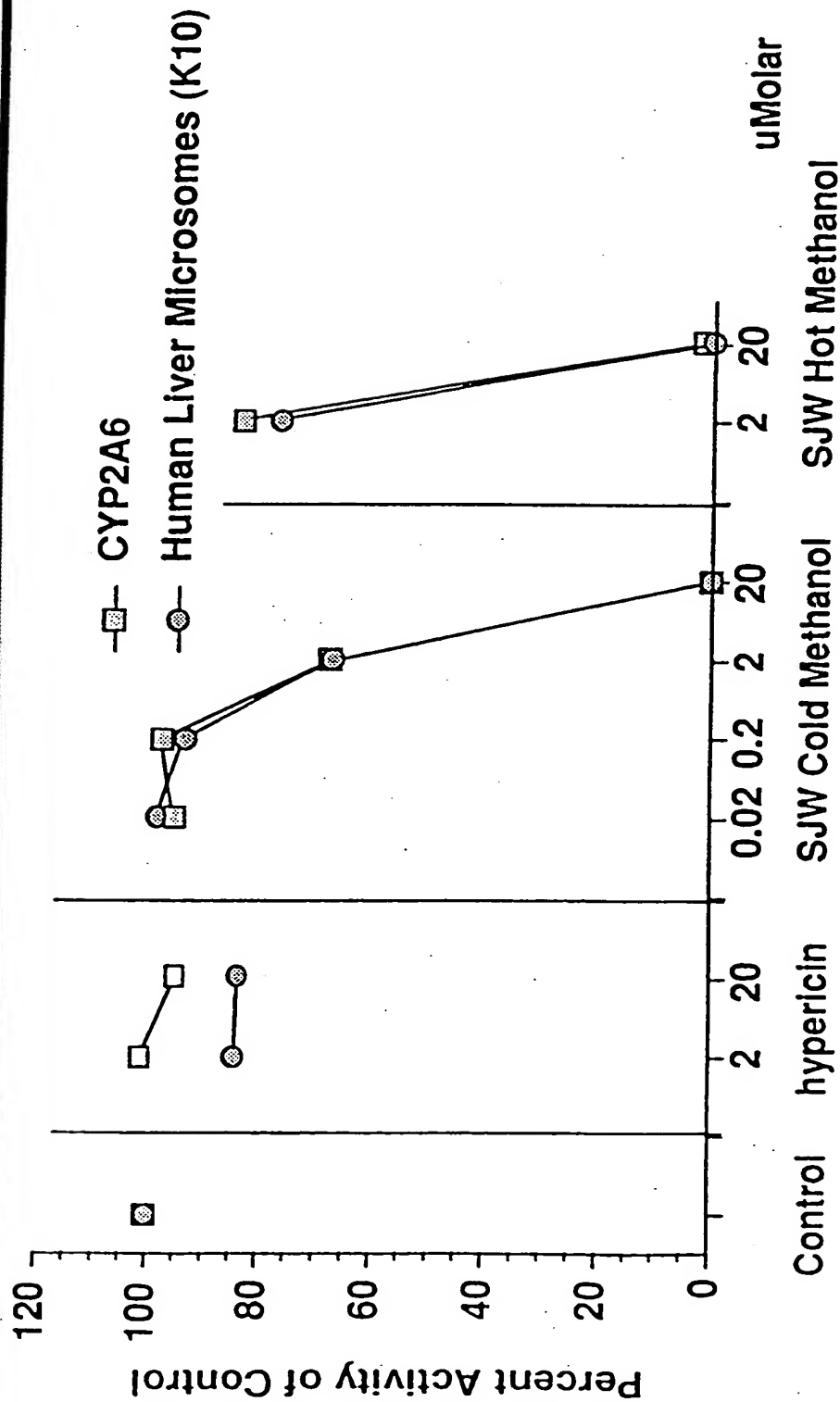


FIGURE 17

# St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo

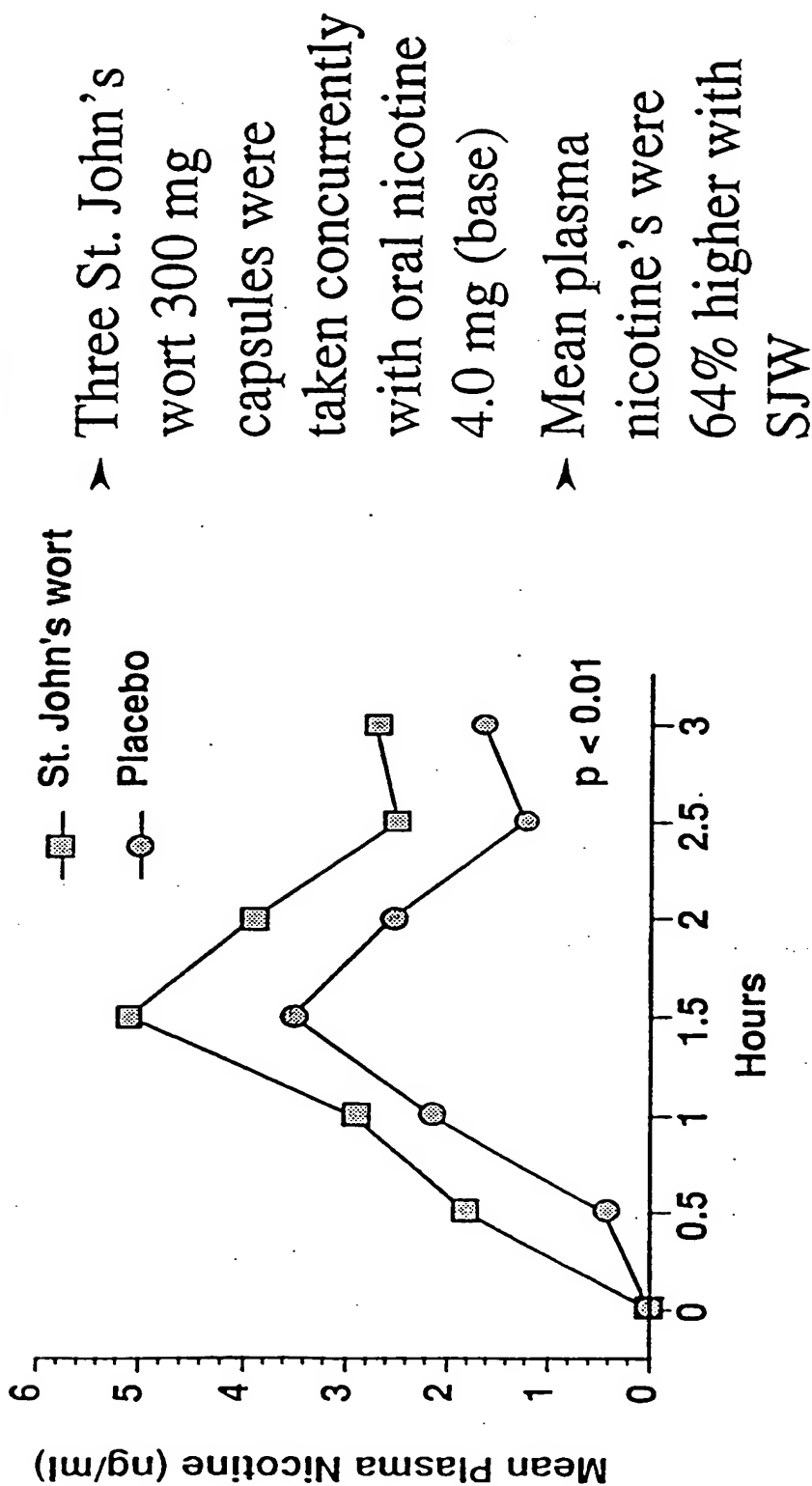
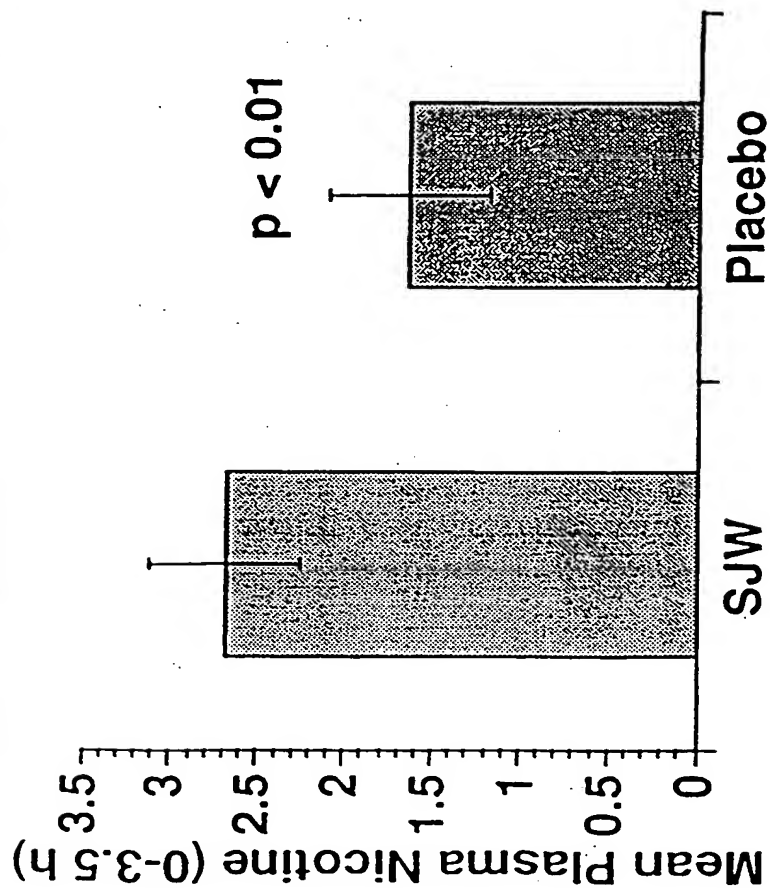


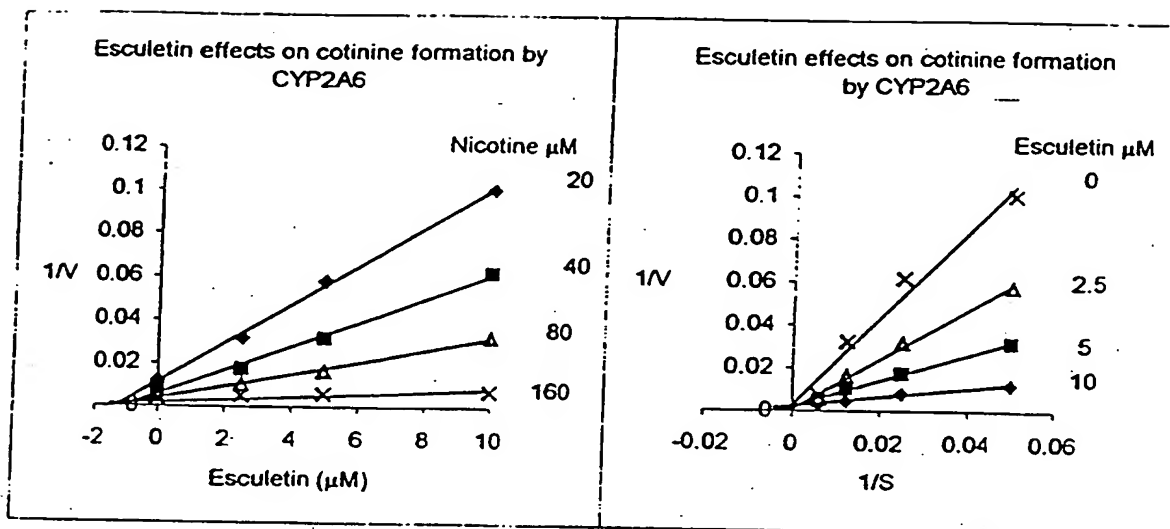
FIGURE 18

# St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo

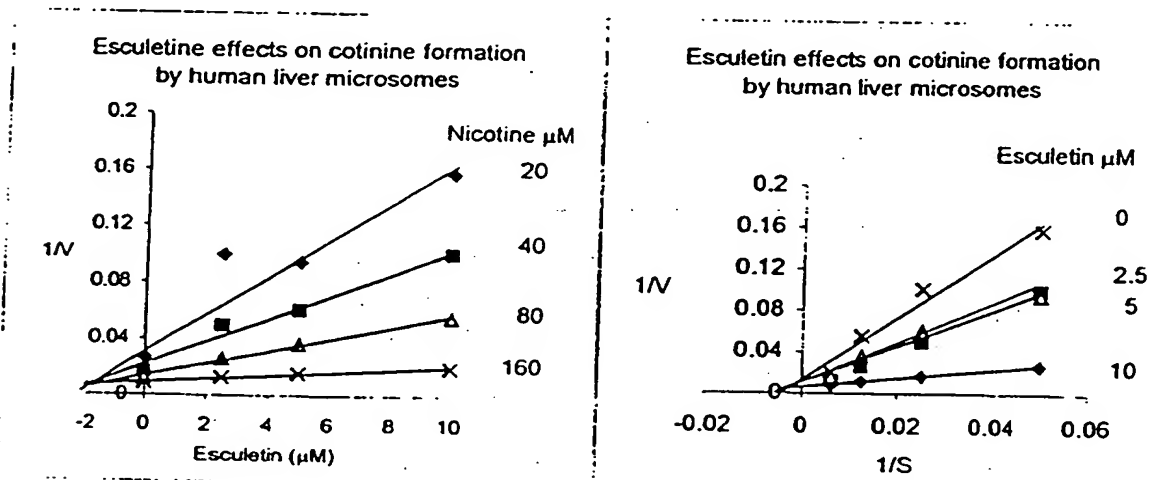


- > Three St. John's wort 300 mg capsules were taken concurrently with oral nicotine 4.0 mg (base)
- > Mean plasma nicotine's were 64% higher with SJW

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**FIGURE 19**

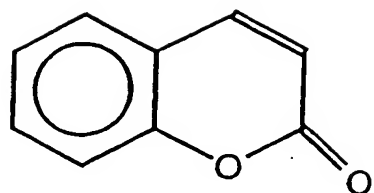


**Estimated  $K_i = 1 \mu M$**   
**Calculated by PCS program  $K_i = 1.1 \mu M$**

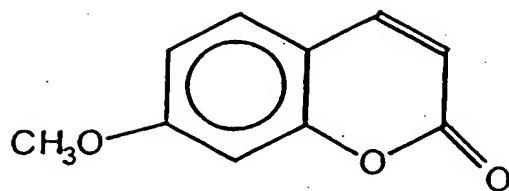


**Estimated  $K_i = 2 \mu M$**   
**Calculated by PCS program  $K_i = 1.6 \mu M$**

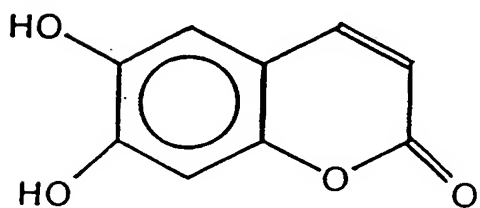
23/23  
FIGURE 20



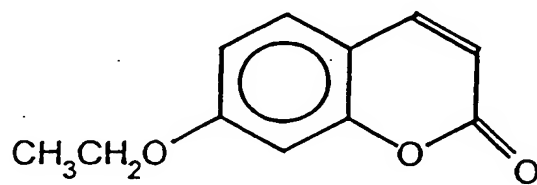
Coumarin



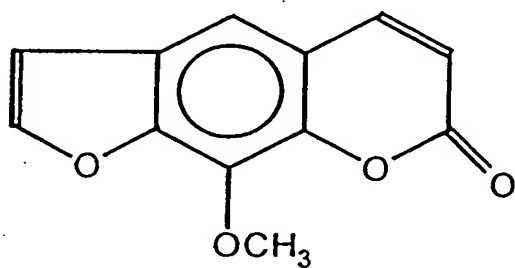
7-Methoxycoumarin



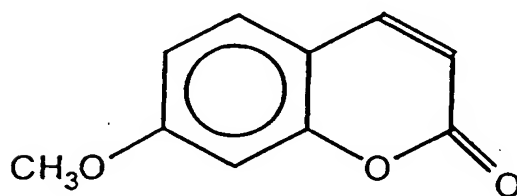
Esculetin



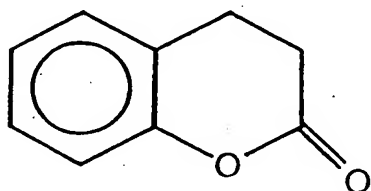
7-Ethoxycoumarin



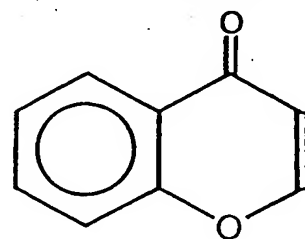
Methoxsalen



7-Methylcoumarin



Dihydrocoumarin



Chromone